

Interaction between tramadol and selective serotonin reuptake inhibitors: are doctors aware of potential risks in their prescription practice?

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ABSTRACT

Objectives The combination of a selective serotonin reuptake inhibitor (SSRI) or serotonin–norepinephrine reuptake inhibitor (SNRI) with tramadol can result in serotonin syndrome, characterised by neuromuscular and autonomic nervous system excitation and altered mental state. The incidence of serotonin syndrome with this combination of drugs is low, and the serotonin syndrome is generally mild or moderate in form, but can be life threatening and is more easily prevented than treated. We aimed to investigate whether prescribers in a general hospital were aware of this risk and if it influenced their prescriptions.

Methods A questionnaire was sent to 194 physicians in a general teaching hospital with over 650 beds in The Netherlands. The questionnaire presented four cases, two of whom used an SSRI or SNRI among other medications, and asked the respondents to prescribe an opioid in each case. The respondents were not aware of the focus of our research. Actual prescription rates of tramadol in admitted patients who did or did not use an SSRI or SNRI were assessed using the hospital pharmacy database.

Results Based on the questionnaire, respondents prescribed tramadol equally in patients with or without concomitant use of SSRIs/SNRIs. About one-third of respondents who prescribed tramadol indicated they were aware of the potential interaction with SSRIs/SNRIs. About one-fifth deliberately avoided tramadol because a potential interaction with SSRIs/SNRIs was identified. However, there was no difference in actual tramadol prescriptions, as recorded in the hospital pharmacy database: 23.8% of SSRI/SNRI users received tramadol versus 24.6% of non-SSRI/SNRI-users (calculated OR 0.96; 95% CI 0.78 to 1.17).

Conclusions In total, 20–30% of prescribers in a general hospital were aware of the potential interaction between tramadol and SSRIs or SNRIs, yet this did not translate to a difference in tramadol prescriptions between SSRI/SNRI users and non-users, as documented in the hospital pharmacy database. A physician's decision to prescribe tramadol to SSRI/SNRI users may be guided by a comprehensive individual benefit–risk assessment; expected benefits of tramadol may outweigh the small risk of serotonin syndrome. In order to increase awareness of the potential risk of a serotonin syndrome, hospital pharmacies may play an important role in signalling the potential interaction and providing information on the benefits and risks of tramadol and alternative analgesics in the presence of SSRIs or SNRIs.

INTRODUCTION

The combination of a selective serotonin reuptake inhibitor (SSRI) or serotonin–norepinephrine reuptake inhibitor (SNRI) with tramadol can result in serotonin syndrome,^{1–12} a syndrome characterised by neuromuscular excitation, autonomic nervous system excitation and altered mental state.¹³ The incidence of serotonin syndrome with this combination of drugs is low, and the serotonin syndrome is generally mild or moderate in form, but can potentially be life threatening. The supposed mechanism by which tramadol, when combined with an SSRI or an SNRI, may lead to serotonin syndrome is not entirely clear. An additive effect has been suggested as tramadol decreases the postsynaptic reuptake of serotonin, as do SSRIs and SNRIs.^{14 15}

It appears that not all opioid agents carry this risk. For example, there are no published case reports that describe serotonin syndrome as a result of an SSRI or SNRI combined with morphine. However, combinations with fentanyl, oxycodone and meperidine (pethidine) have all been associated with serotonin syndrome in case reports.^{16–27} Judging from the number of published case reports, it appears that problems with tramadol are the most frequent.

The serotonin syndrome is more easily prevented than treated. Potential treatments include sedation to reduce muscle hyperactivity, active cooling and serotonin antagonists to reduce hyperthermia.²⁸ Most overview articles consider awareness of the serotonin syndrome the most important step to prevent it,^{13 14 28} yet research among general practitioners showed that a mere 15% were aware of this potentially dangerous syndrome.²⁹

We aimed to investigate whether prescribers in a general hospital were aware of the potential risk of serotonin syndrome as the result of an interaction between tramadol and SSRIs or SNRIs, and if it influenced their prescribing behaviour in clinical practice.

METHODS

The study was performed in the Canisius-Wilhelmina Hospital, a general teaching hospital with over 650 beds in Nijmegen, The Netherlands. Computerised physician order entry is used in this hospital but interaction alerts are not directly communicated to the prescriber but instead judged by the hospital pharmacist and, if necessary, communicated to the physician. A questionnaire



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Table 1 Characteristics of respondents

	No (%) (n=71)
Position	
Medical specialist	31 (44)
Resident	33 (46)
Physician assistant	7 (10)
Specialty	
Anaesthesiology	5 (7)
Cardiology	5 (7)
Emergency medicine	3 (4)
Gastroenterology	2 (3)
Intensive care	3 (4)
Internal medicine	26 (37)
Neurology	3 (4)
Pulmonology	7 (10)
Surgical medicine	10 (14)
Urology	2 (3)
Other*	5 (7)

*Other=geriatric medicine, orthopaedic surgery, gynaecology, neurosurgery and psychiatry.

was sent by email to 138 medical specialists, 47 medical residents and 9 physician assistants. A reminder was sent after 2 weeks. The questionnaire presented four patients, two of whom used citalopram or venlafaxine among several other medications, and two of whom did not use an SSRI or SNRI. Respondents were asked to prescribe an opioid in each case. They were then asked if they had deliberately avoided a specific opioid and whether an interaction between the chosen opioid and any of the patient's medications was identified. The respondents were not aware of the focus of the research on the potential risk of serotonin syndrome due to the combination of tramadol and an SSRI or SNRI.

Next, actual prescription rates of tramadol in patients who did or did not use an SSRI or SNRI were explored. We used the database of the hospital pharmacy of the Canisius-Wilhelmina Hospital. This database contains prescriptions per hospital admission and patient characteristics, such as sex and age. All hospital admissions in 2011 of patients that used any opioid were selected. These admissions were divided in two groups: patients who used an SSRI or SNRI and patients who did not use an SSRI or SNRI. The difference in tramadol prescriptions was evaluated.

We used descriptive analyses to report the results of the questionnaire. The χ^2 test was used to investigate differences in opioid prescriptions between cases with and cases without an SSRI or SNRI. The OR was calculated to compare the tramadol

prescriptions between admitted patients with or without an SSRI or SNRI. Data were analysed with SPSS V.20.0.

The need for informed consent was waived by the local research ethics committee since the study made use of observational anonymised data (registration number 2013/260, local research ethics committee Arnhem-Nijmegen, The Netherlands).

RESULTS

Eighty-nine people (46%) returned the questionnaire. Eighteen respondents who filled in their position and specialty but did not answer any of the other questions were excluded. Thus 71 questionnaires were analysed (table 1).

Table 2 shows the opioids that respondents prescribed in the different cases.

Oxycodone was most often prescribed (68%), followed by tramadol (16%) and morphine (12%). A χ^2 test did not show a significant difference in the frequency of tramadol prescriptions between the cases. About one-third of respondents who prescribed tramadol indicated that they were aware of the interaction with citalopram or venlafaxine. Of the respondents who did not prescribe tramadol, about one-fifth had deliberately avoided tramadol because an interaction with citalopram or venlafaxine was identified. Thus in total, 20–30% of respondents were aware of the potential interaction risk. However, based on the database of the hospital pharmacy, there was no difference in actual tramadol prescriptions: 23.8% of 537 admitted patients who used an SSRI or SNRI received tramadol versus 24.6% of 13 652 admitted patients who did not use an SSRI or SNRI (figure 1). The calculated OR was 0.96 (95% CI 0.78 to 1.17).

In conclusion, both the analysis of the responses to the questionnaire and the analysis of the hospital pharmacy database led similarly to the result that the prescription of tramadol was independent of concomitant use of SSRIs or SNRIs.

DISCUSSION

The combination of tramadol and SSRIs or SNRIs can result in the serotonin syndrome, which is potentially dangerous but easily avoidable if prescribers are aware of this risk. Our research showed that only 20–30% of prescribers in a general hospital were aware of the potential interaction between tramadol and SSRIs or SNRIs, and this knowledge did not translate to a difference in tramadol prescriptions in clinical practice. One can argue that there need not be a difference in prescriptions, as long as prescribers are able to make a risk–benefit assessment and, if necessary, monitor their patients for symptoms, but our results suggest that most prescribers are not aware of the potential risk.

This research has limitations. The response rate to the questionnaire was low. The people who responded may be a

Table 2 Preferred opioid in the four cases presented in the questionnaire

	Patient No 1 using citalopram (n=71)	Patient No 2 using venlafaxine (n=56)	Patient No 3 without SSRI or SNRI (n=64)	Patient No 4 without SSRI or SNRI (n=54)
Tramadol (n (%))	13 (18)	6 (11)	11 (17)	9 (17)
Oxycodone (n (%))	48 (68)	39 (70)	43 (67)	36 (67)
Morphine (n (%))	8 (11)	7 (13)	8 (13)	7 (13)
Fentanyl (n (%))	1 (1)	3 (5)	1 (2)	1 (2)
Buprenorphine (n (%))	1 (1)	1 (2)	1 (2)	1 (2)

SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

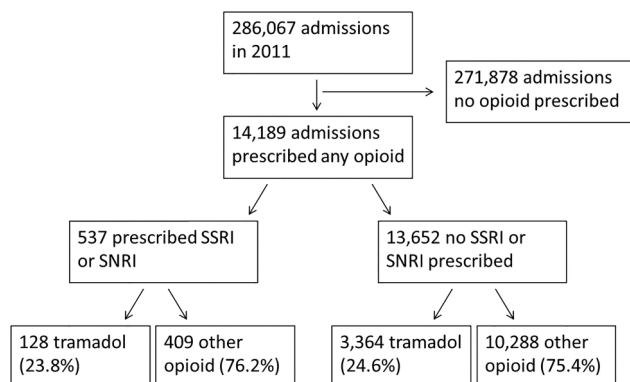


Figure 1 Prescriptions of tramadol during hospital admission in patients who did use and who did not use a selective serotonin reuptake inhibitor (SSRI) or a serotonin–norepinephrine reuptake inhibitor (SNRI).

selection of prescribers who have more than average interest in pharmacotherapy and may have more than average knowledge about interactions. However, if this is the case, our results would have overestimated rather than underestimated the awareness of prescribers. Our hospital pharmacy database does not register home prescriptions. It is possible that admitted patients already used the combination of tramadol and an SSRI or SNRI and that this combination was continued during hospital admission. However, this does not exempt the physician (assistant) from the need to assess potential risks of pharmacotherapy and weighing them against potential benefits.

Overview articles state that the key to prevention is to increase awareness, without specifying the means to achieve this increase. If we assume that our results are representative of other general hospitals, it appears that an encouraging improvement is still to be achieved. Education could be one way to enhance the knowledge of prescribers, but additionally, hospital pharmacies could play an important role. They can signal the

interaction and point out the increased risk of serotonin syndrome to the prescriber or advise about alternative medications.

In conclusion, most prescribers were not aware of the potential interaction between tramadol and SSRIs or SNRIs. Physicians should be able to make an individual risk–benefit assessment if they prescribe tramadol to a patient that concomitantly uses an SSRI or SNRI (eg, if the expected benefits outweigh the small risk of serotonin syndrome, and taking into consideration the characteristic safety profile of potential alternative analgesics). We envision an important role for hospital pharmacies in providing information on the benefit and risks of tramadol and alternative analgesics in the presence of SSRIs or SNRIs.

Competing interests None declared.

Ethics approval The study was approved by the local research ethics committee of Arnhem-Nijmegen, The Netherlands.

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Key messages

What is already known on this subject?

- The combination of a selective serotonin reuptake inhibitor or serotonin–norepinephrine reuptake inhibitor with tramadol can result in serotonin syndrome.
- Most overview articles consider awareness of the serotonin syndrome the most important step to prevent it.

What this study adds?

- Between 20% and 30% of prescribers in a general hospital are aware of the potential interaction between tramadol and selective serotonin reuptake inhibitors (SSRIs) or serotonin–norepinephrine reuptake inhibitors (SNRIs).
- This awareness does not translate to a difference in tramadol prescriptions between SSRI/SNRI users and non-users in clinical practice.
- In order to increase the awareness of the potential risk of a serotonin syndrome, hospital pharmacies may play an important role in providing information on the benefits and risks of tramadol and alternative analgesics in the presence of SSRIs or SNRIs.

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